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2018

document version
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citation for published version (APA)
Rauh, S. P. (2018). *Prediction and etiological modelling in epidemiological cohort studies: in type 2 diabetes and in nursing home residents with dementia and pneumonia*. [, Vrije Universiteit Amsterdam].

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Chapter 7

Self-reported hypoglycaemia in patients with type 2 diabetes treated with insulin in the Hoorn Diabetes Care System Cohort, the Netherlands: a prospective cohort study

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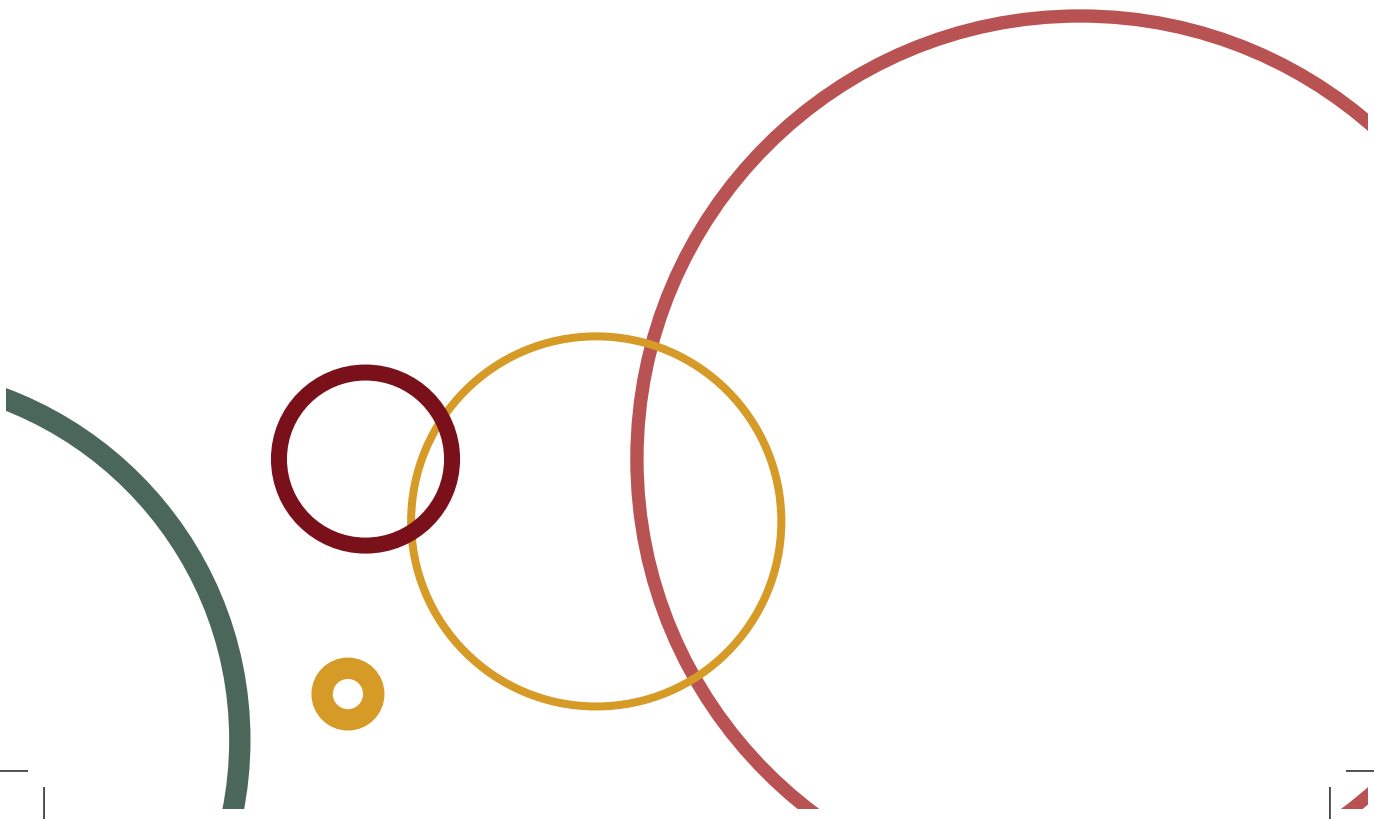
BMJ Open, 2016



ABSTRACT

Background: Our aim was to study the prevalence of self-reported hypoglycaemic sensations and its association with mortality in patients with type 2 diabetes (T2D) treated with insulin in usual care.

Methods: Demographics, clinical characteristics and mortality data were obtained from 1667 patients with T2D treated with insulin in the Hoorn Diabetes Care System Cohort (DCS), a prospective cohort study using clinical care data. Self-reported hypoglycaemic sensations were defined as either mild: events not requiring help; or severe: events requiring help from others (either medical assistance or assistance of others). The association between hypoglycaemic sensations and mortality was analysed using logistic regression analysis.

Results: At baseline, 981 patients (59%) reported no hypoglycaemic sensations in the past year, 612 (37%) reported only mild sensations and 74 (4%) reported severe hypoglycaemic sensations. During a median follow-up of 1.9 years, 98 patients (5.9%) died. Reporting only mild hypoglycaemic sensations was associated with a lower mortality risk (OR 0.48, 95% CI 0.28–0.80), while reporting severe sensations was not significantly associated with mortality (OR 0.76, 95% CI 0.33–1.80), compared with reporting no hypoglycaemic sensations, and adjusting for demographic and clinical characteristics. Sensitivity analyses showed an OR of 1.38 (95% CI 0.31–6.11) for patients reporting severe hypoglycaemic sensations requiring medical assistance.

Conclusion: Self-reported hypoglycaemic sensations are highly prevalent in our insulin-treated T2D population. Patients reporting hypoglycaemic sensations not requiring medical assistance did not have an increased risk of mortality, suggesting that these sensations are not an indicator of increased short-term mortality risk in patients with T2D.

INTRODUCTION

Hypoglycaemic events and hypoglycaemic sensations are major side effects of glucose-lowering therapy in patients with type 2 diabetes (T2D). Hypoglycaemia is associated with a lower quality of life [1, 2] and has been suggested to be associated with an increased risk of cardiovascular events, cardiovascular mortality and all-cause mortality [3-12].

Up until now, the reported prevalence of hypoglycaemia in trials and observational research was mostly based on glucose measurements [3-5, 7-10] and/or based on events registered in medical records [7-10]: hypoglycaemic events. This type of data source might lead to an underestimation of mild hypoglycaemic events – events that can be resolved by the patient without help from others. Moreover, in clinical practice, not all patients with T2D might regularly perform self-testing of their glucose levels and patients consult their general practitioner about experiencing hypoglycaemic sensations without confirmation by glucose measurement. Therefore, self-reported hypoglycaemic sensations might better reflect hypoglycaemia as experienced in everyday life by patients with T2D. However, in the literature, data are lacking on the prevalence of self-reported hypoglycaemic sensations in patients with T2D treated in usual care.

Recently, a prospective study showed that self-reported severe hypoglycaemic sensations were associated with a 3.4-fold increased mortality risk during a 5-year follow-up in ~1000 patients with type 1 and T2D [13]. With regard to self-reported mild hypoglycaemia, conflicting results have been found in different populations: self-reported mild hypoglycaemic sensations were associated with a non-significantly increased mortality risk in the previously mentioned study [13]. In contrast, self-reported mild hypoglycaemia was associated with a significant lower mortality risk in another study in patients with T2D and high cardiovascular risk [4]. These studies used mixed diabetes cohorts with no information available on type of diabetes medication or high-risk groups. Therefore, evidence is needed about the frequency of self-reported mild and severe hypoglycaemic sensations in the general T2D population and the associated mortality risk.

Hypoglycaemic events and sensations are more prevalent in patients with diabetes treated with insulin compared with oral glucose-lowering medication, [14-16] and different mechanisms might play a role in hypoglycaemia in patients treated with different medication types [17]. No previous observational studies have focused on the prevalence of self-reported hypoglycaemic sensations in insulin-treated patients with T2D and its association with mortality. Therefore, the objective of our study was to evaluate the prevalence of self-reported mild and severe hypoglycaemic sensations in insulin-treated patients with T2D treated in usual care, and to investigate the association between self-reported mild and severe hypoglycaemic sensations and mortality.

METHODS

Study population

Data were obtained from the Hoorn Diabetes Care System Cohort, the Netherlands (DCS), a prospective population-based cohort study using clinical care data. Since 1998, patients with T2D living in the region of West-Friesland visit the DCS annually to receive diabetes education – including information on how to recognise hyperglycaemia and hypoglycaemia – and to undergo a physical examination, including the assessment of diabetes-related risk factors and complications. Details on the DCS care system have been described previously [18]. Since 2010, the annual visit includes questions concerning hypoglycaemic sensations in the past year.

For the current study, patients were included when they visited the DCS in 2010, 2011 or 2012 after being treated with insulin for at least 1 year (N=1832). When no data on self-reported hypoglycaemic sensations were available, patients were excluded (N=165). We defined the baseline visit as the first annual visit after the patient had been using insulin for at least 1 year. The baseline visit could therefore contain data from the 2010, 2011 or 2012 visit and patients could have one, two or three measurements of self-reported hypoglycaemic sensations during follow-up. When no questions on hypoglycaemic sensations were answered at the first annual visit after the patient had been using insulin for at least 1 year, this visit was not taken into account and the next annual visit was considered the baseline visit.

Measures

Hypoglycaemic sensations were self-reported in an interview by a medical assistant and were determined using the following questions: did you experience hypoglycaemia in the past year (yes/no)? If yes, what kind of symptoms did you experience: dizziness, dreaming, feeling restless, headache when getting out of bed, hunger, mood swings, palpitations, snoring, sweating during the night, tingling sensations around the mouth, trembling or other. Also, if yes: how many hypoglycaemic events did you experience where help from others was not needed (number per year/ per month/ per week / per day)? How many hypoglycaemic events did you experience that required help from others (number per year/ per month/ per week / per day)? If help was required: was medical assistance needed or was assistance of others needed? Measurements of blood glucose levels were not available.

Mild hypoglycaemic sensations were defined as hypoglycaemic events not requiring help from others. *Severe hypoglycaemic sensations* were defined as events requiring help from others, that is, either medical assistance or assistance of others [18, 19]. Patients were divided into three categories: patients who reported no hypoglycaemic sensations, only mild hypoglycaemic sensations or any severe hypoglycaemic sensations during follow-up.

Information on *mortality* date was derived from the Municipal Personal Records Database up to 1 January 2013. No information on cause of death was available.
Information on current *medication use* was registered by checking dispensing labels brought by patients. Type of insulin was categorised in two groups based on the Anatomical Therapeutic Chemical Classification System (ATC-codes) [20] : (1) only intermediate/long acting (A10AC or A10AE); (2) combination of fast and intermediate/long acting (either A10AD or a combination of fast acting (A10AB) and intermediate/long acting (A10AC or A10AE)).

Weight, height, systolic blood pressure (SBP), diastolic blood pressure (DBP), retinopathy, glycated haemoglobin (HbA1c) levels and urinary albumin-creatinine (UAC) ratio were measured in a standardised way as described previously [18].

Hypertension was defined as an SBP ≥140 mm Hg, a DBP ≥90mm Hg or use of antihypertensive medication. *Retinopathy* was divided into three categories: no retinopathy (EURODIAB [21] grade 0), mild retinopathy (grade 1–3) and severe retinopathy (grade 4–5). *Estimated glomerular filtration rate* (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula.

Cardiovascular history was self-reported: at the first visit to the DCS, patients were asked if they have ever experienced a cerebral vascular accident (CVA), myocardial infarction (MI) or transient ischemic attack (TIA). At all annual visits, patients were asked about events in the past year. Cardiovascular history was dichotomised (yes/no; CVA, MI or TIA before baseline). *Smoking* was self-reported (no/former/current smoking) and was dichotomised in former+current/no. *Diabetes duration* was reported by the patient's general practitioner. *Socioeconomic status* (SES) was self-reported based on highest completed educational level and was categorised into three groups: low (no completed education/primary education/secondary education – practical training); middle (prevocational secondary education/vocational training/general secondary education or pre-university education); and high (professional university education/university).

Statistical analysis

Baseline prevalence of mild and severe self-reported hypoglycaemic sensations is presented as number and percentage. Baseline characteristics are presented as number and percentage, mean±SD or median (IQR) for skewed distributions. Characteristics are shown for the total population and stratified for type of self-reported hypoglycaemic sensations during follow-up. Differences between groups were tested using independent samples Student's t-tests (continuous variables), Mann-Whitney's U tests (skewed distributions) and χ^2 statistics (dichotomous and categorical variables), including tests for trends for ordinal categorical variables.

Logistic regression analysis was used to analyse the association between hypoglycaemic sensations and mortality. Adjusted models were constructed adjusting for sex and baseline values of age, diabetes duration, SES, body mass index (BMI), HbA1c,

smoking, hypertension, use of metformin, use of sulfonylurea (SU), retinopathy, eGFR, UAC ratio and cardiovascular disease (CVD) history. For continuous confounders, linearity was checked and, if necessary, variables were categorised. Since the number of events limited adjusting for all these possible confounders in one model, separate models were constructed correcting for one confounder at a time. Additionally, one model was constructed with a combination of confounders, adjusting for sex, age, diabetes duration (</≥10 years), HbA1c level (</≥7% (53 mmol/mol)), hypertension, smoking, use of SU and microvascular or macrovascular complications (yes/no), defined as either having retinopathy, CVD history, an eGFR value <60 or a UAC ratio ≥3.5 mg/mmol for women or ≥2.5 mg/mmol for men.

All statistical analyses were performed using IBM SPSS statistics V.20.

Sensitivity analyses

The first sensitivity analysis distinguished between severe hypoglycaemic sensations requiring non-medical or medical assistance.

Second, the combination of mild and severe hypoglycaemic sensations was studied by categorising type of self-reported hypoglycaemic sensations in four categories: no hypoglycaemic sensations, only mild, both mild and severe, or only severe hypoglycaemic sensations during follow-up.

Third, it has been suggested that frequent mild hypoglycaemic events might protect against the effects of a severe hypoglycaemic event [3]. Therefore, we evaluated whether a dose-response association was observed between mortality and the average number of reported mild hypoglycaemic events per year, in quartiles. For this analysis, only patients who did not report severe hypoglycaemic sensations were taken into account. In addition, to rule out a possible survival effect, we evaluated whether a dose-response association was observed when only taking into account the number of reported mild hypoglycaemic events reported at baseline, again in quartiles.

Fourth, we evaluated whether differences in follow-up duration between patients affected the results. Therefore, generalised linear models with follow-up duration on the natural logarithmic scale as an offset variable were introduced in the models.

Fifth, patients who had missing values on all questions regarding hypoglycaemic sensations at the first annual visit after they had been using insulin for at least 1 year were excluded from the analyses.

Finally, we checked for possible interaction between mild and severe hypoglycaemic sensations, and between hypoglycaemic sensations and cardiovascular history (yes/no), age (</≥70 years), sex and use of SU.

RESULTS

Population characteristics

The mean age at baseline was 67.2 years (SD: 11.7 years), 47% (N=784) were women and the mean duration of diabetes at baseline was 11.5 years (IQR: 7.9–15.9 years). The characteristics of the total population and those stratified for type of hypoglycaemic sensations reported during follow-up are summarised in Table 1. Compared with the patients who reported no hypoglycaemic sensations during follow-up, patients reporting hypoglycaemic sensations had a significantly longer diabetes duration, longer duration of insulin use, longer follow-up duration, and were more often treated with a combination of both fast-acting and intermediate-acting/long-acting insulin, while there were no significant differences in glycaemic control. In addition, patients reporting only mild hypoglycaemic sensations were significantly younger, more often used only metformin next to their insulin, less often used only SU next to their insulin, and had a lower mortality rate.

Prevalence of hypoglycaemic sensations

Figure 1 shows that at baseline, 59% of the patients (N=981) reported that they experienced no hypoglycaemic sensations during the last year, 37% (N=612) reported only mild hypoglycaemic sensations, 3% (N=55) reported only severe hypoglycaemic sensations and 1% (N=19) reported both mild and severe hypoglycaemic sensations.

During a median follow-up of 1.9 years (IQR: 1.1–2.4 years), 48% of the patients (N=804) reported no hypoglycaemic sensations (Table 1), 45% (N=744) reported only mild hypoglycaemic sensations and 7% (N=119) reported severe hypoglycaemic sensations. Of the latter group, 50% (N=59) also reported mild hypoglycaemic sensations during follow-up, while the others (N=60) only reported severe hypoglycaemic sensations.

Hypoglycaemic sensations and mortality

During follow-up, 5.9% of the patients died (N=98). Patients who died during follow-up were significantly older at baseline (mean 75.9 vs 66.7 years old) compared with patients who were still alive at the end of follow-up, but did not significantly differ in diabetes duration or HbA1c levels at baseline (data not shown).

Table 1: Patient characteristics according to severity of hypoglycaemia during follow-up

	Total group (N=1667)	No hypoglycaemia (N=804 (48%))	Only mild hypoglycaemia (N=744 (45%))	Severe hypoglycaemia (N=119 (7%))
Baseline characteristics				
Age, years	67.2 ± 11.7	68.7 ± 12.2	65.6 ± 11.0*	67.7 ± 12.3
Women	784 (47%)	364 (45%)	357 (48%)	63 (53%)
Diabetes duration, years	11.5 [7.9–15.9]	11.2 [7.3–14.9]	12.0 [8.2–16.5]*	12.1 [8.2–18.4]*
Duration of insulin use, years	4.6 [2.1–7.6]	4.3 [1.8–6.5]	4.9 [2.7–8.7]*	5.5 [3.8–10.1]*
Type of insulin				
Only intermediate/long acting	714 (43%)	419 (52%)	266 (36%)*	29 (24%)*
Combination fast and intermediate/long	885 (53%)	341 (42%)	459 (62%)*	85 (71%)*
Use of oral antidiabetic medication (next to insulin)				
No oral antidiabetic medication	416 (25%)	177 (22%)	194 (26%)	45 (38%)*
Only metformin	642 (39%)	285 (35%)	305 (41%)*	52 (44%)
Only SU	95 (6%)	65 (8%)	29 (4%)*	1 (1%)*
Metformin and SU	449 (27%)	238 (30%)	190 (26%)	21 (18%)*
Other [a]	65 (4%)	39 (5%)	26 (3%)	0
HbA1c, % (mmol/mol)	7.6 ± 1.2 (60 ± 13)	7.6 ± 1.2 (60 ± 12)	7.5 ± 1.1 (58 ± 12)	7.8 ± 1.3 (62 ± 14)
BMI, kg/m^2	31.3 ± 5.9	31.6 ± 5.8	31.2 ± 5.9	30.5 ± 6.2
Smoking	342 (21%)	160 (20%)	156 (21%)	26 (22%)
UAC ratio, mg/mmol	2.0 [0.8–6.4]	2.1 [0.9–6.9]	1.9 [0.8–5.9]	2.3 [0.8–4.8]
eGFR	80.3 ± 24.9	79.6 ± 25.9	81.2 ± 23.3	79.3 ± 27.0
Hypertension [b]	1411 (85%)	685 (85%)	626 (84%)	100 (84%)
Systolic blood pressure, mmHg	144.3 ± 22.1	144.7 ± 22.6	143.9 ± 21.6	143.9 ± 21.7
Diastolic blood pressure, mmHg	76.4 ± 9.3	76.7 ± 10.0	76.2 ± 8.5	75.7 ± 9.1
Use of antihypertensive medication	1222 (73%)	590 (73%)	548 (74%)	84 (71%)
Cardiovascular history [c]	339 (20%)	153 (19%)	156 (21%)	30 (25%)
CVA	65 (4%)	34 (4%)	25 (3%)	6 (5%)
MI	218 (13%)	101 (13%)	98 (13%)	19 (16%)
TIA	99 (6%)	39 (5%)	51 (7%)	9 (8%)
Retinopathy				
No	1164 (70%)	563 (70%)	524 (70%)	77 (65%)*
Mild	78 (5%)	28 (4%)	37 (5%)	13 (11%)
Severe	13 (1%)	7 (1%)	5 (1%)	1 (1%)
Educational level				
Low	786 (47%)	385 (48%)	344 (46%)	57 (48%)
Middle	541 (33%)	234 (29%)	267 (36%)	40 (34%)
High	204 (12%)	97 (12%)	99 (13%)	8 (7%)

Follow-up characteristics				
Number of mild hypoglycaemic events during follow-up (in total group)	0 [0–12]	NA	24 [4–64]	0 [0–24]
Number of patients who reported mild hypoglycaemia during follow-up	803 (48%)	NA	744 (100%)	59 (50%)
Number of mild hypoglycaemic events during follow-up (in patients reporting hypoglycaemia)	24 [5–65]	NA	24 [4–64]	24 [12–101]
Number of severe hypoglycaemic events during follow-up	0 [0–0]	NA	NA	2 [2–13]
Follow-up duration, years [d]	1.9 [1.1–2.4]	1.8 [1.1–2.3]	1.9 [1.2–2.5]*	2.1 [1.5–2.6]*
Mortality	98 (5.9%)	67 (8.3%)	24 (3.2%)*	7 (5.9%)

Abbreviations: BMI: body mass index; CVA: cerebral vascular accident; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HbA1c: glycated haemoglobin; MI: myocardial infarction; NA: not applicable; SBP: systolic blood pressure; SU: sulfonylurea; TIA: transient ischemic attack; UAC: urinary albumin-creatinine.
Data are presented as numbers (%), mean ± SD or median [IQR].

* Significantly different ($p<0.05$) compared with the patients who reported no hypoglycaemia during follow-up; differences in characteristics between the groups were tested using χ^2 for dichotomous and nominal categorical variables, using χ^2 including tests for trends for ordinal categorical variables, using independent-samples Student's t-tests for continuous variables, and Mann-Whitney's U tests for continuous variables that were not normally distributed.

[a] Other oral antidiabetic medication = other than metformin and SU, whether or not combined with metformin and/or SU.

[b] Hypertension is defined as either an SBP ≥140 mm Hg, a DBP ≥90mm Hg or use of antihypertensive medication.

[c] Patients can be in more than one subcategory if they have experienced more than one type of cardiovascular event.

[d] Follow-up duration is defined as either the time between baseline and 1/1/2013, or, if someone died before 1/1/2013, as the time between baseline and mortality.

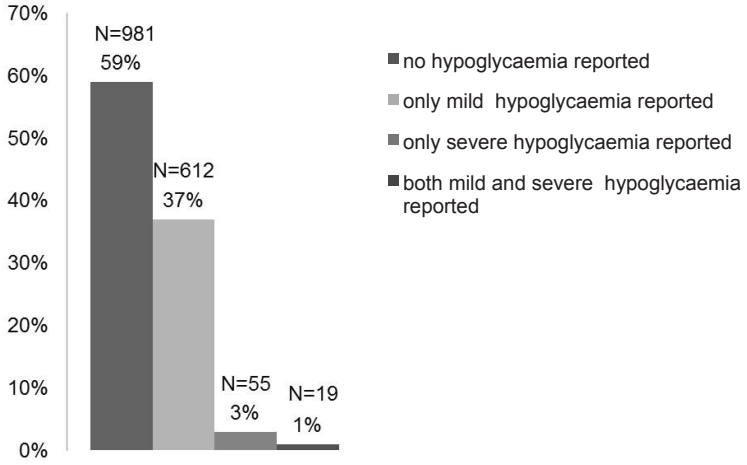


Figure 1: Baseline prevalence of self-reported hypoglycaemia

Table 2: Association between hypoglycaemia and mortality

	OR (95% CI)	P value
Crude model		
No hypoglycaemia during follow-up	[Reference]	
Only mild hypoglycaemia during follow-up	0.37 (0.23–0.59)	<0.01
Severe hypoglycaemia during follow-up	0.69 (0.31–1.54)	0.36
Adjusted model [a]		
No hypoglycaemia during follow-up	[Reference]	
Only mild hypoglycaemia during follow-up	0.48 (0.28–0.80)	<0.01
Severe hypoglycaemia during follow-up	0.76 (0.33–1.80)	0.52

Abbreviations: CVD: cardiovascular disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HbA1c: glycated haemoglobin; SBP: systolic blood pressure; UACR: urinary albumin-creatinine ratio.

[a] Adjusted for age, sex, diabetes duration (</≥10 years), HbA1c level (<7%(<53 mmol/mol) / ≥7%(53 mmol/mol)), hypertension (SBP≥140 mm Hg, DBP≥90 mm Hg or use of antihypertensive medication), smoking, use of sulfonylurea, and microvascular or macrovascular complications (defined as retinopathy, history of CVD, eGFR value <60 or UACR ≥3.5 mg/mmol for women or ≥2.5 mg/mmol for men)

The results of the logistic regression analyses are presented in Table 2. Reporting only mild hypoglycaemic sensations was significantly associated with a lower mortality risk during follow-up (OR 0.37, 95% CI 0.23–0.59), compared with reporting no hypoglycaemic sensations, while reporting severe hypoglycaemic sensations was non-significantly associated with a lower mortality risk (OR 0.69, 95% CI 0.31–1.54). After univariate adjustment for possible confounders, the lower mortality risk in the group reporting mild hypoglycaemic sensations remained significant in all models and the OR in the group reporting severe hypoglycaemic sensations remained non-significant (data not shown). After multivariate adjustment for age, sex, diabetes duration, HbA1c level, hypertension, smoking, use of SU and microvascular and macrovascular complications, the ORs for mortality during follow-up were 0.48 (95% CI 0.28–0.80) and 0.76 (95% CI 0.33–1.80), respectively, for patients reporting only mild hypoglycaemic sensations and patients reporting severe hypoglycaemic sensations, compared with patients reporting no hypoglycaemic sensations during follow-up.

Sensitivity analyses

Reporting severe hypoglycaemic sensations, but not requiring medical help, was non-significantly associated with a lower mortality risk (OR 0.57, 95% CI 0.23–1.46), while reporting severe hypoglycaemic sensations requiring medical assistance was non-significantly associated with a higher mortality risk (OR 1.38, 95% CI 0.31–6.11; Table 3A), compared with patients reporting no hypoglycaemic sensations. Compared with the total group of patients who reported severe hypoglycaemic sensations, patients reporting severe hypoglycaemic sensations that required medical help were on average older, more often male, had a longer diabetes duration, a longer duration of insulin use, higher HbA1c levels, a lower BMI and a higher mortality rate (see Supplementary Table A).

Second, reporting both mild and severe hypoglycaemic sensations was non-significantly associated with a lower mortality risk (OR 0.39, 95% CI 0.09–1.62), while reporting only severe hypoglycaemic sensations was not associated with mortality (OR 1.00, 95% CI 0.39–2.58; Table 3B), compared with patients reporting no hypoglycaemic sensations.

Third, sensitivity analyses showed lower ORs on mortality for patients reporting more mild events during follow-up (Table 3C), as well as when only mild events reported at baseline were taken into account.

Generalised linear models with follow-up duration as an offset variable showed that differences in follow-up duration between patients did not influence the results (data not shown).

Excluding patients who had missing values on all questions regarding hypoglycaemic sensations at the first annual visit after they had been using insulin for at least 1 year (N=405) did not change our results (data not shown).

Finally, no significant interaction was observed between mild and severe hypoglycaemic sensations, or between hypoglycaemic sensations and cardiovascular history, age </≥70 years, sex, or use of SU.

Table 3: Sensitivity analyses

(A) Association between mortality and hypoglycaemia, whether or not requiring medical help

	OR (95% CI)	P value
No hypoglycaemia during follow-up	[Reference]	
Only mild hypoglycaemia during follow-up	0.37 (0.23–0.59)	<0.01
Severe hypoglycaemia during follow-up, but no medical help reported	0.57 (0.23–1.46)	0.24
Severe hypoglycaemia during follow-up, requiring medical help	1.38 (0.31–6.11)	0.68

(B) Association between mild and severe hypoglycaemia, whether or not combined with mild hypoglycaemia, and mortality

	OR (95% CI)	P value
No hypoglycaemia during follow-up	[Reference]	
Only mild hypoglycaemia during follow-up	0.37 (0.23–0.59)	<0.01
Mild and severe hypoglycaemia during follow-up	0.39 (0.09–1.62)	0.19
Only severe hypoglycaemia during follow-up	1.00 (0.39–2.58)	1.00

(C) Dose-response association between mild hypoglycaemia and mortality

	OR (95% CI)	P value
Number of events reported during follow-up [a,b]		
No hypoglycaemia during follow-up	[Reference]	
≤2 mild hypoglycaemic events per year	0.52 (0.23–1.16)	0.11
3–10 mild hypoglycaemic events per year	0.52 (0.22–1.22)	0.13
12–32 mild hypoglycaemic events per year	0.38 (0.16–0.88)	0.03
≥33 mild hypoglycaemic events per year	0.14 (0.04–0.59)	<0.01
Number of events reported at baseline [a,c]		
No hypoglycaemia	[Reference]	
≤2 mild hypoglycaemic events	0.72 (0.30–1.68)	0.44
3–11 mild hypoglycaemic events	0.66 (0.26–1.67)	0.38
12–48 mild hypoglycaemic events	0.29 (0.11–0.81)	0.02
≥52 mild hypoglycaemic events	0.30 (0.09–0.97)	0.04

[a] Only patients who did not report severe hypoglycaemia were taken into account.

[b] For this analysis, the average number of mild hypoglycaemic events per year was calculated by dividing the total number of reported mild events during follow-up by the number of measurements. This number was categorised based on quartiles.

[c] For this analysis, the number of hypoglycaemic events reported at baseline was categorised based on quartiles.

DISCUSSION

In this prospective cohort study among 1667 insulin-treated patients with T2D from usual care, we found that 37% of the patients reported mild hypoglycaemic sensations during the past year, while 4% reported severe hypoglycaemic sensations. These numbers are somewhat lower compared with previous studies in which 51%–64% reported mild hypoglycaemia and 7%–25% severe hypoglycaemia [16], or 50% reported any hypoglycaemia [22]. In line with earlier studies, we observed that patients reporting hypoglycaemic sensations had a longer duration of diabetes as well as insulin use [16, 22, 23], and were more often treated with fast-acting insulin [24].

In addition, we observed that patients with mild hypoglycaemic sensations had a 50% lower mortality risk during follow-up, compared with those without hypoglycaemic sensations. This finding is in line with previous studies on objectively measured [3] and self-reported mild hypoglycaemia [4], but contradictory to other studies, which showed (non-significant) higher mortality rates for objectively measured [5] and self-reported mild hypoglycaemia [13]. These discrepancies might be explained by differences in diabetes duration, or the type of diabetes treatment, type of diabetes and care setting.

Surprisingly, we observed that severe hypoglycaemic sensations were also (non-significantly) associated with a lower risk on mortality during follow-up, compared with those without hypoglycaemic sensations. However, sensitivity analyses showed that this association could mainly be attributed to the patients who experienced both mild and severe hypoglycaemic sensations. Moreover, reporting severe hypoglycaemic sensations requiring medical assistance was associated (although not significant) with a 40% higher mortality risk. This positive association between hypoglycaemic sensations requiring medical help and mortality is in line with previous studies [3-5, 7-11, 13]. The fact that this association was non-significant in our study could be due to the low number of patients reporting this type of event.

One mechanism that could explain our observed association between hypoglycaemic sensations not requiring medical help and mortality is a protective effect of frequent mild hypoglycaemia against the effects of a severe hypoglycaemic event [3]. However, although we observed a supporting dose-response association, we did not find an interaction between mild and severe hypoglycaemic sensations. Another mechanism could be impaired awareness of hypoglycaemia [25]: experiencing mild hypoglycaemic sensations could increase the patients' awareness regarding their risk on hypoglycaemia and other diabetes complications, which in turn might positively affect their health behaviour and reduce their mortality risk; while impaired awareness could prevent patients from taking actions to resolve their hypoglycaemia. This mechanism is supported by previous studies showing that impaired awareness is associated with increased incidence of severe hypoglycaemia [25, 26]. More research is, however, needed to verify this possible mechanism.

Our study has some limitations that warrant discussion. Our study was observational; therefore, direct causal relationships cannot be established, and unmeasured confounding might have influenced the results. Second, we asked the patients about hypoglycaemic sensations during the past year, which might have led to an underestimation of the prevalence of hypoglycaemic sensations [27]. Third, we did not objectively measure hypoglycaemia. It might be that some patients confused, for instance, 'normal feelings' of hunger with mild hypoglycaemia, or that some patients experienced pseudo-hypoglycaemia. However, we think that for clinical practice it is very relevant to also look at patient-reported hypoglycaemic sensations rather than objectively measured events only. Finally, we were unable to take the cause of death into account and the size of our population did not permit correction for all possible confounders combined. However, in a full corrected model, the association was slightly attenuated but still statistically significant.

The strengths of our study include the representative population to evaluate the incidence of hypoglycaemic sensations in patients with T2D treated with insulin, as well as the use of self-reported hypoglycaemic sensations, which might better reflect hypoglycaemic sensations as experienced in everyday life than the use of objectively measured events only, the fact that several sensitivity analyses were performed to study the association between mild and severe hypoglycaemic sensations and mortality, and the prospective design with repeated measurements of the exposure.

We believe that our results are relevant for clinical practice. While we studied patient-reported hypoglycaemic sensations rather than objectively measured events only, we showed that self-reported hypoglycaemic sensations are highly prevalent in the insulin-treated T2D population, and that self-reported hypoglycaemic sensations not requiring medical assistance are not associated with an increased risk of mortality, suggesting that these sensations are not an indicator of increased short-term mortality risk in patients with T2D.

We would, however, like to emphasise that hypoglycaemia can be troublesome for patients and that hypoglycaemia and fear of hypoglycaemia have been shown to reduce quality of life [28]. For future research, it is important to further study the different associations with mortality of self-reported hypoglycaemic sensations compared with objectively measured events.

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SUPPLEMENTARY TABLE A:

Characteristics of patients reporting any severe hypoglycaemia versus severe hypoglycaemia requiring medical help

	Severe hypoglycaemia – total (N=119)	Severe hypoglycaemia – subgroup requiring medical help (N=18)
Baseline characteristics		
Age, years	67.7 ± 12.3	70.2 ± 13.1
Women	63 (53%)	7 (39%)
Diabetes duration, years	12.1 [8.2–18.4]	13.3 [10.6–19.0]
Duration of insulin use, years	5.5 [3.8–10.1]	6.4 [3.3–10.9]
Use of oral anti-diabetic medication (next to insulin)		
No oral anti-diabetic medication	45 (38%)	7 (39%)
Only metformin	52 (44%)	9 (50%)
Only SU	1 (1%)	1 (6%)
Metformin and SU	21 (18%)	1 (6%)
Other [a]	0	0
HbA1c, % (mmol/mol)	7.8 ± 1.3 (62 ± 14)	8.4 ± 1.3
BMI, kg/m^2	30.5 ± 6.2	29.4 ± 6.5
Hypertension [b]	100 (84%)	15 (83%)
Cardiovascular history	30 (25%)	7 (39%)
Follow-up characteristics		
Follow-up duration, years [c]	2.1 [1.5–2.6]	2.2 [1.4–2.4]
Mortality	7 (5.9%)	2 (11.1%)

Data are presented as numbers (%), mean ± SD or median [IQR]. SU: sulfonylurea

[a] Other oral anti-diabetic medication = other than metformin and SU, whether or not combined with metformin and/or SU

[b] Hypertension is defined as either a SBP ≥140 mmHg, a DBP ≥90mmHg, or use of anti-hypertensive medication

[c] Follow-up duration is defined as either time between baseline and 1/1/2013, or, if someone died before 1/1/2013, as time between baseline and mortality